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# Synthesis of Vancomycin from the Aglycon

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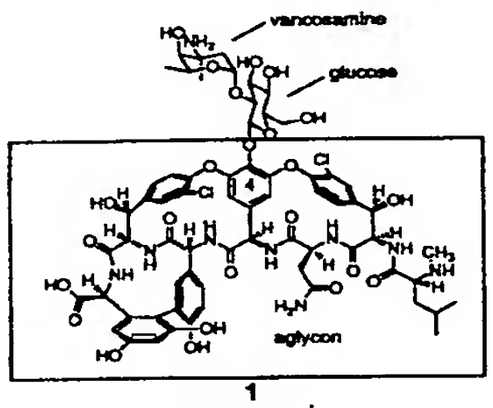
**Abstract:** Vancomycin-resistant bacterial strains pose a serious threat to human health. Efforts to overcome vancomycin resistance by modifying the natural product have shown that the carbohydrates help modulate biological activity. To explore the mechanisms by which the carbohydrates function, it would be useful to have access to vancomycin derivatives containing different disaccharides. We now describe the synthesis of vancomycin from a readily available protected aglycon. This chemistry lays the groundwork for wide-ranging investigations of the roles of the carbohydrates in the biological activity of vancomycin. Moreover, in developing methods to glycosylate vancomcyin, we have extended the utility of the sulfoxide glycosylation reaction considerably by making it possible to use unhindered esters as neighboring groups. The chemistry we describe may also have implications for how to improve some other glycosylation methods.

## Introduction

Vancomycin (**1**, Figure 1) is a glycopeptide antibiotic used to treat methicillin-resistant Gram-positive infections. Vancomycin-resistant bacterial strains pose a serious threat to human health. Efforts to overcome vancomycin resistance by modifying the natural product have shown that the carbohydrates help modulate antibiotic activity. In fact, dramatic increases in activity against vancomycin-resistant microorganisms can be produced simply by attaching substituents to the C3 nitrogen of the vancosamine sugar.[1] Since vancomycin resistance arises from a change in the dipeptide substrate that weakens its affinity for the vancomycin binding pocket, it is not clear how modifying the sugars, which do not contact the substrate, can lead to improvements in activity.[2] To explore the mechanisms by which the carbohydrates function, it would be useful to have access to vancomycin derivatives containing different carbohydrate moieties.[3] We recently reported chemistry to attach the vancosamine sugar to the pseudoaglycon of vancomycin.[3c] We now describe the synthesis of vancomycin from a readily available protected aglycon. This chemistry lays the groundwork for wide-ranging investigations of the roles played by the carbohydrates of vancomycin in biological activity. Moreover, in developing methods to glycosylate vancomycin, we have extended the utility of the sulfoxide glycosylation reaction considerably by making it possible to use unhindered esters as neighboring groups. The solution we describe may also have implications for how to improve some other glycosylation methods. Finally, now that Evans and Nicolaou have finished making the aglycon,[4] this work formally completes the total synthesis of vancomycin.




**1**
vancomycin

**Figure 1.** Glycopeptide antibiotic vancomycin.

## Background

To construct vancomycin from the aglycon, we needed a good method to make the glycosidic linkage to the 2,4,6-trisubstituted phenol of amino acid 4 on the aglycon. A wide variety of natural products contain glycosidic linkages to phenols.[5] Because phenols are not very good nucleophiles, successful glycosylation usually requires basic conditions that generate the more reactive phenolates.[5a,b,6] One widely used approach to make glycosidic linkages to phenols involves the $S_N2$ displacement of anomeric

(1) The carbohydrates on vancomycin have been implicated in biological activity. See, for example: (a) Rodriguez, M. J.; Snyder, N. J.; Zweifel, M. J.; Wilkie, S. C.; Stack, D. R.; Cooper, R. D.; Nicas, T. I.; Mullen, D. L.; Butler, T. F.; Thompson, R. C. *J. Antibiot.* **1998**, *51*, 560. (b) Malabarba, A.; Nicas, T. I.; Thompson, R. C. *Med. Res. Rev.* **1997**, *17*, 69. (c) Williams, D. H. *Nat. Prod. Rep.* **1996**, 469.

(2) (a) Walsh, C. T.; Fisher, S. L.; Park, I.-S.; Prahalad, M.; Wu, Z. *Chem. Biol.* **1996**, *3*, 21. For various hypotheses on how carbohydrate derivatives of vancomycin can overcome bacterial resistance, see, for example: (b) Sharman, G. J.; Try, A. C.; Dancer, R. J.; Cho, Y. R.; Staroske, T.; Bardsley, B.; Maguire, A. J.; Cooper, M. A.; O'Brien, D. P.; Williams, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 12041. (c) Allen, N. E.; Le Tourneau, D. L.; Hobbs, J. N. *J. Antibiot.* **1997**, *50*, 677.

(3) The vancomycin disaccharide has been synthesized by three different groups but has never been attached to the aglycon: (a) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 3471. (b) Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rubsam, F.; Rodriguez, R. M. *Angew. Chem.* **1998**, *110*, 1972. (c) Ge, M.; Thompson, C.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 11014.

(4) (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700. (b) Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2717. For other synthetic efforts toward the vancomycin aglycon, see: (c) Boger, D. L.; Beresis, R. T.; Loiseleur, O.; Wu, J. H.; Castle, S. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 721. (d) Rama Rao, R. V.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135.

(5) (a) Stachulski, A. V.; Jenkins, G. N. *Nat. Prod. Rep.* **1998**, 173. (b) Gonzalez, G. I.; Zhu, J. *J. Org. Chem.* **1997**, *62*, 7544. (c) Yoshioka, T.; Aizawa, Y.; Fujita, T.; Nakamura, K.; Sasahara, K.; Kuwano, H.; Kinoshita, T.; Horikoshi, H. *Chem. Pharm. Bull.* **1991**, *39*, 2124.

(6) (a) Conchie, J.; Levvy, G. A.; Marsh, C. A. *Adv. Carbohydr. Chem.* **1957**, *12*, 157. (b) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961.

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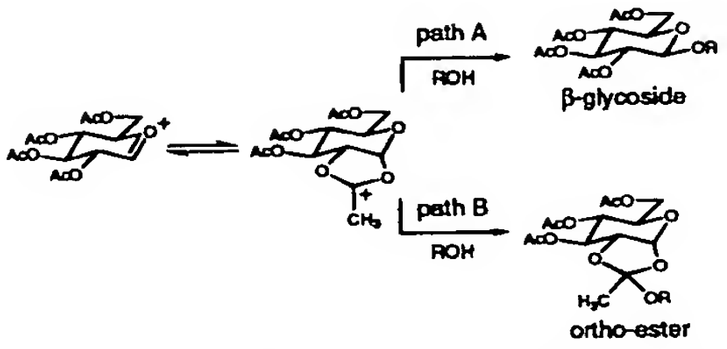
**Scheme 1**[a]




[a] Trapping on the anomeric carbon of activated glycosyl donors containing neighboring group esters leads to the desired $\beta$-glycosides (path A). Trapping on the carbonyl carbon leads to ortho ester side products (path B).

halides under basic conditions. Although this approach often works well with unhindered phenolates, elimination of the anomeric halide becomes a serious problem with hindered phenolates.[5a,7] Unfortunately, the aglycon of vancomycin is both sterically hindered and highly sensitive to base.[8,9] Under the basic conditions typically used for phenol glycosylations, the asparagine side chain would rearrange,[8] and the amino acids could racemize.[4b,10]

The case of vancomycin is further complicated because the glycosidic bond to the phenol is 1,2-trans ($\beta$). The most widely used approach for achieving stereochemical control in the formation of $\beta$-glycosidic linkages involves using a C2 ester capable of neighboring group participation.[11−13] With many glycosylation methods, the presence of a C2 ester group decreases the reactivity of the glycosyl donor considerably. High temperatures and extended reaction times are required in order to activate the donor and achieve glycosylation.[12] Under these conditions, decomposition processes begin to dominate the reaction, particularly when weakly nucleophilic acceptors are used.

An advantage of the sulfoxide glycosylation method is that donor activation takes place readily at low temperatures under mild conditions, even in the presence of electron-withdrawing protecting groups.[14] Unless the C2 ester is a pivaloate or comparably hindered neighboring group, however, ortho ester formation occurs instead of glycosylation (Scheme 1).[15] Unfortunately, the use of pivaloate esters as protecting groups is not compatible with the synthesis of vancomycin because the conditions (basic or reductive) required for deprotection are too harsh.[8,9b] Furthermore, because pivaloates sometimes impede glycosylations involving hindered nucleophiles, they can be problematic neighboring groups, even for substrates that can withstand harsh deprotection conditions. The need to use pivaloates as neighboring groups has been a significant limitation of the sulfoxide glycosylation method. In the course of exploring ways to glycosylate vancomycin, we have overcome this limitation by finding a better way to suppress ortho ester formation that permits the use of unhindered esters as neighboring groups.

## Results and Discussion

The fact that ortho ester formation dominates in the sulfoxide glycosylation reaction when acetates are used as protecting groups has puzzled us for many years. Acetates have been used successfully with many other glycosylation methods that also appear to go through an oxonium ion intermediate (e.g., trichloroimidate donors).[12] In considering possible explanations for the different outcomes, it occurred to us that most glycosylation methods that work well with acetates as neighboring groups employ Lewis acid catalysts such as $BF_3$.[12] It has long been known that Lewis acids catalyze the rearrangement of ortho esters to the corresponding $\beta$-glycosides.[11,16] Therefore, we reasoned that including $BF_3$ in the sulfoxide glycosylation reaction might suppress ortho ester formation and make it possible to use acetates as neighboring groups. Unfortunately, preliminary attempts to glycosylate a protected vancomycin aglycon with several different glucose sulfoxides in the presence of $BF_3$ and $Tf_2O$, conditions previously used to attach the vancosamine sugar to the vancomycin pseudoaglycon,[3c] gave no product.

This result was not entirely unexpected. A model study involving the glycosylation of 2,6-dimethoxyphenol had shown that no product was obtained unless 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was included in the reaction (compare entry 1 with entry 2, Table 1). The base presumably increases the nucleophilicity of the phenol sufficiently to permit glycosylation.[17] Since we could not avoid the use of base, we decided to try the reaction in the presence of *both* $BF_3$ and DTBMP. Brown and Kanner have shown that sterically hindered pyridine bases prefer protic over Lewis acids.[18] Therefore, we thought that there was a reasonable chance that the base would perform its function of increasing the nucleophilicity of the phenol while the Lewis acid would suppress ortho ester formation. We confirmed that glycosylation of the hindered phenol model system with the perpivaloated glucosyl donor could be achieved in the presence of $BF_3$ if base was included in the reaction. As hoped, the addition of $BF_3$ did not interfere with the function of the base (Table 1, entry 3).

We next examined whether the presence of $BF_3$ would suppress ortho ester formation. As shown in Table 1, glycosy-

(7) Strongly acidic conditions have also been used to form glycosidic linkages to phenols, but yields can be low and stereoselectivity poor; see ref 3c.

(8) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915.

(9) Vancomycin is also sensitive to acidic and oxidative conditions, see: (a) Nagarajan, R.; Schabel, A. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1306. (b) Adamczyk, M.; Grote, J.; Rege, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 885 and references therein.

(10) The vancomycin aglycon has been enzymatically glycosylated: Solenberg, P. J.; Matsushima, P.; Stack, D. R.; Wilkie, S. C.; Thompson, R. C.; Baltz, R. H. *Chem. Biol.* **1997**, *4*, 195.

(11) Wulff, G.; Rohle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157.

(12) For a review on glycosylation methodology, see: Toshima, K.; Tatsuta, K. *Chem Rev.* **1993**, *93*, 1503.

(13) Danishefsky has developed a good method for making 1,2-trans linkages to phenols that involves nucleophilic attack on a 1,2-epoxy sugar by a potassium phenolate. Glycosylation of a variety of phenols has been demonstrated, but we did not feel that the strong basic conditions would be amenable to vancomycin, see ref 3a. 2,6-Dimethoxyphenol has been glycosylated using a trichloroimidate; the reaction required 24 h at room temperature, see ref 3b.

(14) (a) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881. (b) Kim, S.-H.; Augeri, D.; Yang, D.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 1766. (c) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524. (d) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518.

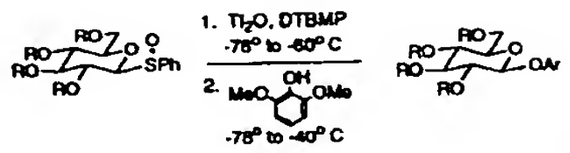
(15) (a) Kunz, H.; Harreus, A. *Liebigs Ann. Chem.* **1982**, 41. (b) Sato, S.; Nunomura, S.; Nakano, T.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *33*, 4097. (c) Seeberger, P. H.; Eckhardt, M.; Gutteridge, C. E.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10064.

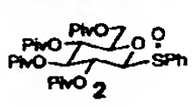
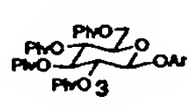
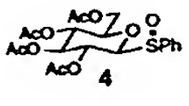
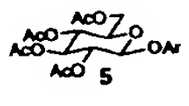
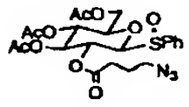
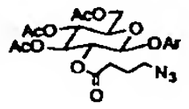
(16) Wang, W.; Kong, F. *J. Org. Chem.* **1998**, *63*, 5744.

(17) Under the conditions of entry 1 (Table 1), the $\beta$-glycoside is formed stereospecifically. Although this outcome might have been anticipated on the basis of our previous experience with similar nucleophiles,[5a,b] Crich has reported mixtures of $\alpha$- and $\beta$-phenylglycosides when hindered phenols are glycosylated with pivaloated glycosyl sulfides activated with PHSOTf. Crich has argued that glycosyl sulfides activated with PHSOTf and glycosyl sulfoxides activated with $Tf_2O$ both generate anomeric triflates. However, in cases involving neighboring group participation, these glycosylation methods evidently do not react via the same intermediates since they produce different stereochemical outcomes. See: (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435. (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.

(18) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1953**, *75*, 3865.

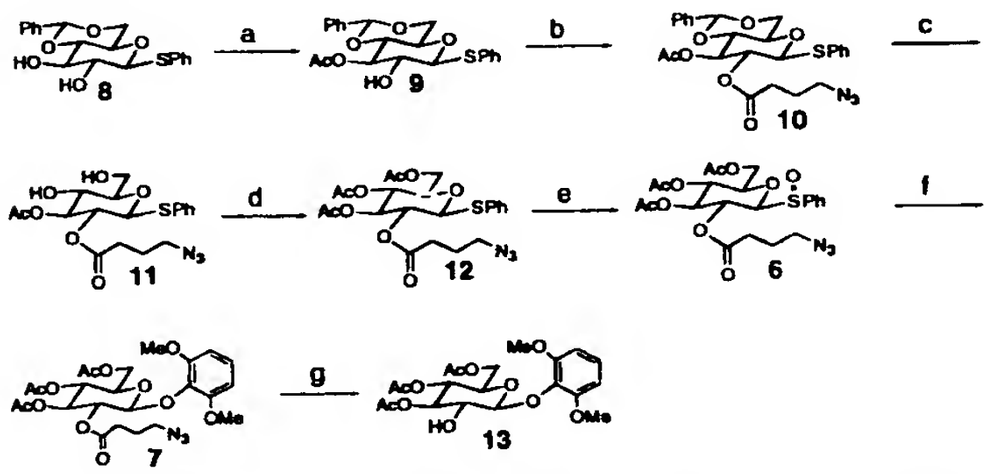
**Table 1**




| Entry[a] | Sulfoxide | Product | $BF_3$ | Yield |
|---|---|---|---|---|
| 1 |  2 |  3 | – | 50% |
| 2[b] | 2 | 3 | – | 0% |
| 3 | 2 | 3 | + | 46% |
| 4 |  4 |  5 | + | 56% |
| 5 | 4 | 5 | – | 14%[c] |
| 6 |  6 |  7 | + | 62% |

[a] Glycosylations were performed by adding $Tf_2O$ (2 equiv) to the sulfoxide (2 equiv) and 2,6-di-*tert*-butylmethylpyridine (4 equiv) at −78 °C in $CH_2Cl_2$, allowing the reaction to warm to −60 °C for 20 min, and adding the 2,6-dimethoxyphenol (1 equiv) as a solution in $CH_2Cl_2$ with or without $BF_3$ (10 equiv). The reaction was then warmed to −40 °C and quenched with saturated $NaHCO_3$. [b] 2,6-Di-*tert*-butylmethylpyridine (DTBMP) omitted from reaction. [c] The major product was the ortho ester (21%).

**Scheme 2**[a]

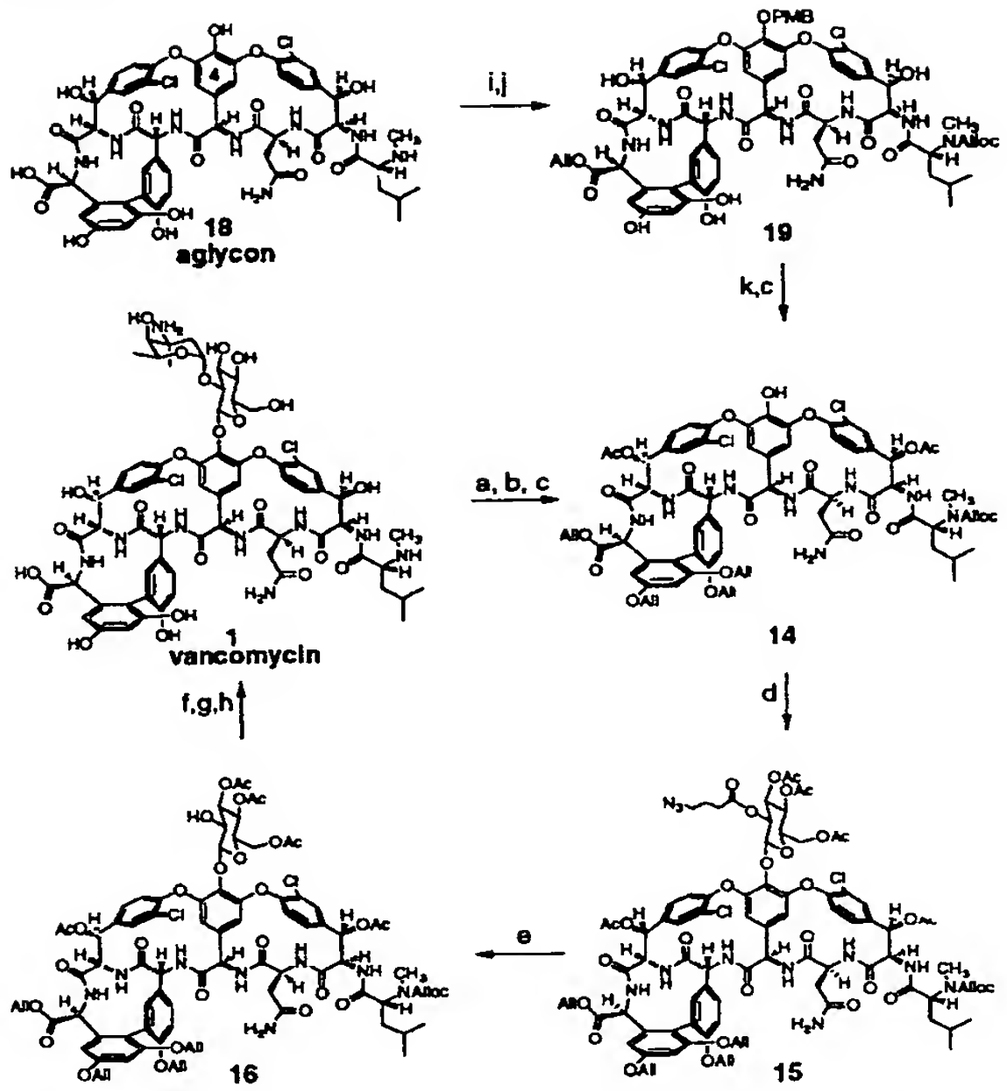



[a] Conditions: (a) (1) $Bu_2SnO$, benzene, reflux, 12 h; (2) AcCl, $CH_2Cl_2$, 0 °C, 2 h, 83% (8:1 C3 acetate:C2 acetate); (b) 4-azidobutyric acid, oxalyl chloride, DMF (catalytic), $CH_2Cl_2$, 0 °C to rt, 3 h, then **9**, pyridine, $CH_2Cl_2$, rt 1 h, 94%; (c) *p*-toluenesulfonic acid, $CH_2Cl_2$:MeOH 1:3, rt 15 h, 82%; (d) AcCl, pyridine, $CH_2Cl_2$, 0 °C to rt, 2 h, 100%; (e) *m*-CPBA, $CH_2Cl_2$, −78 to 0 °C, 2 h, 98%; (f) $Tf_2O$, DTBMP, $CH_2Cl_2$, −78 to −60 °C, 20 min, then 2,6-dimethoxyphenol and $BF_3$·$Et_2O$, −78 to −55 °C, 45 min, 62%; (g) $Ph_3P$, $H_2O$, dioxane, reflux, 3 h, 64%.

lation of the hindered phenol model system with peracetylated glucose sulfoxide took place with complete stereochemical control and in good yield in the presence of both $BF_3$ and DTBMP (compare entries 4 and 5, Table 1). The chemistry also worked well when sulfoxide **6** (Scheme 2), which contains an azidobutyryl group at C2,[19] was used to glycosylate the model phenol (entry 6, Table 1). This neighboring group was investigated because azidobutyryl esters can be removed under conditions that do not cleave acetates.[19] We found that the azidobutyryl phenyl glycoside **7** can be deprotected to **13** in 64% yield with $Ph_3P$ in refluxing dioxane/$H_2O$ (Scheme 2), conditions that were expected to be compatible with the entire range of protecting groups and functionality on the vancomycin pseudoaglycon. Thus, we finally had an approach to $\beta$-glycosylate the weakly nucleophilic phenol on the vancomycin aglycon using a neighboring group that could be deprotected selectively under mild conditions.

(19) Kusumoto, S.; Sakai, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1296.

**Scheme 3**[a]




[a] Conditions: (a) (i) 4 equiv of alloc-succinimide, 3 equiv of $NaHCO_3$, $H_2O$/dioxane, rt, 3 h; (ii) 5 equiv of allyl bromide, 2 equiv of $NaHCO_3$, DMF, rt, 2 h; (iii) 10 equiv of allyl bromide, 5 equiv of $Cs_2CO_3$, DMF, rt, 6 h; (iv) 10 equiv of PhSH, 1% HBr/HOAc, rt, 15 min, 63%, four steps; (b) 2 equiv of $Cs_2CO_3$, 5 equiv of PMBCl, DMF, rt, 12 h, 98%; (c) (i) 18 equiv of $Ac_2O$, 36 equiv of pyridine, 0.2 equiv of DMAP, $CH_2Cl_2$, rt, 5 h; (ii) 10% TFA in $CH_2Cl_2$, rt, 10 min, 95%, 2 steps; (d) 3.2 equiv of **6**, 3.2 equiv of $Tf_2O$, 6.5 equiv of DTBMP, $CH_2Cl_2$, −78 to −60 °C, 30 min, then 1 equiv of **14** and 20 equiv of $BF_3$·$Et_2O$, −78 to 0 °C, 1.5 h; (e) 4 equiv of $Ph_3P$, 5:1 dioxane:$H_2O$, reflux, 2 h, 13%, 2 steps; (f) 2 equiv of $BF_3$·$Et_2O$, 2 equiv of $Tf_2O$, $CH_2Cl_2$, then 4 equiv of **17** (Scheme 4), $Et_2O$, −78 to −20 °C, 1 h, 60% plus 23% recovered **16**; (g) 5% hydrazine, allyl alcohol:MeOH:THF = 1:1:1, rt, 4 h, 63%; (h) 50 equiv of $Bu_3SnH$, 1 equiv of $PdCl_2(PPh_3)_3$, DMF:AcOH 1:1, rt, 10 min, 78%; (i) (i) 2 equiv of alloc-succinimide, 2 equiv of $NaHCO_3$, $H_2O$/dioxane, rt, 2 h; (ii) 2 equiv of allyl bromide, 2 equiv of $KHCO_3$, DMF, rt, 1 h, 40% over two steps; (j) 5 equiv of PMBCl, 10 equiv of $Cs_2CO_3$, DMF, rt, 2 h, 70%; (k) 20 equiv of allyl bromide, 50 equiv of $Cs_2CO_3$, molecular sieves, DMF, rt, 6 h, 60%.

Although success in a model system is encouraging, the scope of a method can be evaluated only when it is applied to a real system. Accordingly, **14** was prepared from vancomycin (**1**) in 59% yield over seven steps (Scheme 3). Following protection of the amines, the carboxylic acid, and the phenols, the glycosidic linkage to the aglycon was hydrolyzed using 1% HBr/HOAc and thiophenol.[20] The liberated phenol was temporarily protected as a *p*-methoxybenzyl ether and was regenerated to give **14** after acetylation of the two benzylic hydroxyls.

Treatment of **14** with sulfoxide **6** and triflic anhydride in the presence of DTBMP and $BF_3$ gave **15**,[21] the identity of which

(20) Ten equivalents of thiophenol was used to scavenge the cleaved sugars, which prevents byproduct formation and the loss of protecting groups from the aglycon.

(21) **15** could not be completely purified, but the mass (ESI) was consistent with the structure shown.

was verified after removal of the azidobutryl group by correlation to a previously characterized degradation product of vancomycin (**16**).[3c] Following HPLC purification, the yield for the two-step sequence was 13%. If we assume a 60−65% yield for removal of the azidobutyryl group, based on the studies in the much simpler model system **7**, the estimated yield for the glycosylation of **2** is 20−25%. This is lower than the 62% yield obtained for glycosylation in the model system; given the difficulty of the case, however, we were pleased that the reaction worked at all.

The synthesis of vancomycin was completed in three steps as shown in Scheme 3.[3c] We have previously described the chemistry to form the α-glycosidic linkage to the vancosamine sugar using the sulfoxide glycosylation method.[3c] $BF_3$ was used in this glycosylation in order to suppress dehydradation of the primary asparagine amide in vancomycin. Hence, including $BF_3$ in the sulfoxide glycosylation reaction extends its utility to acceptors containing amides and also permits the use of unhindered esters such as acetates as neighboring groups.

For those interested in the total synthesis of vancomycin, we note that it is possible to arrive at the protected aglycon **14** from the known aglycon of vancomycin **18** (Scheme 3).[22] Following protection of the amine and the carboxylic acid as shown, the phenol of amino acid 4 of the aglycon can be selectively protected[23] with *p*-methoxylbenzyl chloride and cesium carbonate in the presence of the other three phenols and the two alcohols to give **19**. The remaining phenols can then be alkylated with allyl bromide, and the benzylic alcohols can be acetylated. Finally, the *p*-methoxybenzyl ether can be selectively removed to give the desired protected aglycon **14**. Now that Evans and Nicolaou have reported their landmark syntheses of the vancomycin aglycon,[4] the work described here completes a formal total synthesis of this elusive target.

## Conclusion

The chemistry described above extends the utility of the sulfoxide glycosylation reaction significantly by making it possible to use unhindered esters for β-glycoside formation. Although pivaloate groups are effective at preventing ortho ester formation, they introduce a new set of problems because they are difficult to install and remove, which limits their utility to molecules that are relatively stable. In addition, the need to use pivaloate esters to achieve β-glycosylation sometimes results in awkward protecting group manipulations. Therefore, the use of $BF_3$ to suppress ortho ester formation overcomes a significant limitation of the sulfoxide method. Furthermore, our results suggest that other glycosylation methods in which Lewis acid catalysts are employed may benefit from the inclusion of DTBMP or comparable pyridine bases, particularly when poor nucleophiles are used as acceptors.

We note in closing that our primary motivation in developing conditions to attach sugars to vancomycin was to make it possible to study the biochemical roles of the carbohydrates on vancomycin and other glycopeptide antibiotics. Although de novo synthesis is now possible, the protected aglycon **14** can be obtained far more quickly and in multigram quantitites via degradation, as outlined. With methods now available to make *both* glycosidic linkages of vancomycin, we should be able to construct a wide range of carbohydrate derivatives of vancomycin in which the two sugars are independently varied to explore the roles of the sugars in biological activity.

(22) Marshall, F. J. *J. Med. Chem.* **1965**, *8*, 18.
(23) Seneci, P.; Ferrari, P.; Scotti, R.; Ciabatti, R. *J. Antibiot.* **1992**, *45*, 1633.

## Experimental Section

**General Methods.** Unless otherwise stated, all chemicals were purchased from Aldrich or Sigma and used without further purification. Vancomycin was a generous gift from Merck. Methylene chloride, toluene, benzene, pyridine, and triethylamine were distilled from calcium hydride under dry argon. Diethyl ether and tetrahydrofuran were distilled from potassium benzophenone ketyl under dry argon. DMF and ethyl acetate were dried over activated molecular sieves. All air- or moisture-sensitive reactions were run under an atmosphere of dry argon.

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 $F_{254}$ plates (0.25 mm thickness) precoated with a fluorescent indicator. The developed plates were examined under short-wave UV light and stained with anisaldehyde. Flash chromatography[24] was performed using silica gel 60 (230−400 mesh) from EM Science. Radial chromatography was performed on a Chromatatron from Harrison Research using 1-mm circular plates. Analytical HPLC was performed on a Hewlett-Packard Ti Series 1050 instrument. Preparative HPLC was performed using a Hitachi L-6200A pump and a Waters 484 tunable absorbance detector. Vancomycin compounds were monitored at an absorbance wavelength of 285 nm.

NMR spectra were recorded on a JEOL GSX 270-MHz NMR spectrometer or a Varian Inova 500-MHz/VNMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), apparent triplet (apt), broad singlet (bs), pentet (p), and octet (o).

High-resolution mass spectra (FAB) were obtained at the University of California at Riverside Department of Chemistry Mass Spectrometry Facility.

**Phenyl 3-*O*-Acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (9).** Benzene (30 mL) was added to phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside[25] (524.3 mg, 1.45 mmol) and dibutyltin oxide (399.6 mg, 1.6 mmol), and the solution was refluxed with a Dean Stark trap for 6 h. The reaction was then cooled, filtered through Celite, and concentrated. The residue was dissolved in 50 mL of $CH_2Cl_2$ and cooled to 0 °C. AcCl was added (130 μL, 1.81 mmol), and the reaction was stirred at 0 °C for 2 h and then filtered through a plug of silica gel with 100% EtOAc. The filtrate was washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL), dried over $Na_2SO_4$, and concentrated. Purification by flash chromatography (40% EtOAc/petroleum ether) gave 486.0 mg (83%) of **9** as an 8:1 mixture of C3:C2 acetates: $R_f$ 0.53 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.59 (m, 10H), 5.49 (s, 1H, benzylic proton), 5.24 (apt, $J$ = 9 Hz, 1H, H3), 4.69 (d, $J$ = 10 Hz, 1H, H1), 4.39 (dd, $J$ = 11, 4 Hz, 1H, H6), 3.78 (apt, $J$ = 9.5 Hz, 1H, H5), 3.53−3.61 (m, 3H, H6′, H4, H2), 2.73 (s, 1H, C2 OH), 2.12 (s, 3H, C3 acetate); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 171.8, 137.6, 134.0, 131.9, 129.9, 129.3, 129.0, 126.9, 137.6, 134.0, 131.9, 129.9, 129.3, 129.0, 126.9, 102.2, 89.9, 78.9, 75.6, 72.3, 71.5, 69.3, 21.7; HR-MS (FAB) calcd for $C_{21}H_{22}O_6SNa$ [M + $Na^+$] 425.1035, found 425.1032.

**Phenyl 2-(4-Azidobutyryl)-3-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (10).** To a solution of 4-azidobutyric acid[17] (1.2 g, 9.3 mmol) in 35 mL of $CH_2Cl_2$ were added oxalyl chloride (4.4 mL of a 2 M solution in $CH_2Cl_2$, 8.8 mmol) and 4 drops of DMF. The solution was stirred at room temperature for 2.5 h (until the evolution of gas had stopped). Then 21 mL of this azidobutyryl chloride solution was added via syringe to a solution of **9** (481.6 mg, 1.20 mmol) and pyridine (1.94 mL, 23.9 mmol) in 25 mL of $CH_2Cl_2$. The reaction was stirred for 45 min at room temperature and then poured into 100 mL of saturated $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic extracts were combined, washed with 1 N HCl (100 mL) and saturated NaCl (100 mL), dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography in 20% EtOAc/petroleum ether to give 575.5 mg (94%) of **10** as an 8:1 mixture of C2:C3 azidobutyrates: $R_f$ 0.48 (25% EtOAc/

(24) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(25) Liptak, A.; Jodal, I.; Harangi, J.; Nanasi, P. *Acta Chim. Hung.* **1983**, *113*, 415.

petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.33−7.48 (m, 10H), 5.49 (s, 1H, benzylic proton), 5.34 (apt, $J$ = 9.5 Hz, 1H, H3), 5.02 (dd, $J$ = 10, 8.5 Hz, 1H, H2) 4.82 (d, $J$ = 10 Hz, 1H, H1), 4.39 (dd, $J$ = 10.5, 5 Hz, 1H, H6), 3.79 (apt, $J$ = 10 Hz, 1H, H6′), 3.67 (apt, $J$ = 9.5 Hz, 1H, H4), 3.55−3.60 (m, 1H, H5), 3.39 (t, $J$ = 7 Hz, 2H), 2.46 (o, $J$ = 7 Hz, 2H), 2.02 (s, 3H, C3 acetate), 1.92 (p, $J$ = 7 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ 171.5, 170.2, 136.9, 133.1, 131.8, 129.4, 129.3, 128.7, 128.5, 126.4, 101.7, 86.7, 78.3, 73.0, 71.1, 70.9, 68.6, 50.6. 31.2, 24.3, 21.0; HR-MS (FAB) calcd for $C_{25}H_{27}N_3O_7SNa$ [M + $Na^+$] 536.1467, found 536.1491.

**Phenyl 2-(4-Azidobutyryl)-3-*O*-acetyl-1-thio-$\beta$-D-glucopyranoside (11).** Compound **10** (575.5 mg, 1.12 mmol) was dissolved in 40 mL of 3:1 MeOH:$CH_2Cl_2$, and *p*-toluenesulfonic acid (90 mg, 0.473 mmol) was added. The reaction was stirred for 15 h, and then 100 $\mu$L of pyridine was added and the reaction concentrated. Purification of the residue by flash chromatography with 65% EtOAc/petroleum ether removed the minor isomer and gave 389.8 mg (82%) of pure **11**: $R_f$ 0.40 (75% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.32−7.46 (m, 5H), 5.07 (apt, $J$ = 9.5 Hz, 1H, H3), 4.95 (apt, $J$ = 9.5 Hz, 1H, H2), 4.77 (d, $J$ = 10 Hz, 1H, H2), 3.94 (dd, $J$ = 12.0, 3.5 Hz, 1H, H6), 3.83 (dd, $J$ = 12.0, 4.5 Hz, 1H, H6′), 3.74 (apt, $J$ = 9.5 Hz, 1H, H4). 3.45−3.48 (m, 1H, H5), 3.38 (t, $J$ = 7 Hz, 2H), 2.45 (o, $J$ = 7 Hz, 2H), 2.07 (s, 3H, C3 acetate), 1.92 (p, $J$ = 7 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ 171.7, 171.5, 132.7, 132.2, 129.3, 128.5, 86.0, 79.9, 77.2, 70.3, 69.4, 62.4, 50.6, 31.2, 24.3, 21.1; HR-MS (FAB) calcd for $C_{18}H_{23}N_3O_7SNa$ [M + $Na^+$] 448.1154, found 448.1136.

**Phenyl 2-(4-Azidobutyryl)-3,4,6-tri-*O*-acetyl-1-thio-$\beta$-D-glucopyranoside (12).** To a solution of **11** (367.5 mg, 0.864 mmol) at 0 °C in 50 mL of dry $CH_2Cl_2$ were added pyridine (683 $\mu$L, 8.64 mmol) and acetyl chloride (308 $\mu$L, 4.32 mmol). The reaction was allowed to warm to room temperature and quenched with 1 mL of MeOH after 1 h. The reaction was diluted with 300 mL of EtOAc and washed with saturated $NaHCO_3$ (100 mL), 1 N HCl (100 mL), and saturated NaCl (100 mL). The organic layer was dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography with 50% EtOAc/petroleum ether to give 440.2 mg (100%) of **12** as a white solid: $R_f$ 0.56 (50% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.48−7.50 (m, 2H), 7.32−7.33 (m, 3H), 5.24 (apt, $J$ = 10 Hz, 1H, H3), 5.05 (apt, $J$ = 10 Hz, 1H, H4), 4.99 (apt, $J$ = 10 Hz, 1H, H2), 4.72 (d, $J$ = 10.5 Hz, 1H, H1), 4.23 (dd, $J$ = 12, 5 Hz, 1H, H6), 4.18 (dd, $J$ = 12, 2.5 Hz, 1H, H6′), 3.71−3.75 (m, 1H, H5), 3.38 (apt, $J$ = 7 Hz, 2H), 2.45 (o, $J$ = 7 Hz, 2H), 2.09 (s, 3H, acetate), 2.02 (s, 3H, acetate), 1.99 (s, 3H, acetate), 1.92 (p, $J$ = 7 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ 171.2, 170.7, 170.3, 169.5, 133.2, 131.7, 129.1, 128.6, 85.9, 76.0, 74.0, 70.2, 68.4, 62.3, 50.5, 31.1, 24.3, 20.9, 20.7; HR-MS (FAB) calcd for $C_{22}H_{27}N_3O_9SNa$ [M + $Na^+$] 532.1366, found 532.1381.

**Phenyl 2-(4-Azidobutyryl)-3,4,6-tri-*O*-acetyl-1-sulfinyl-$\beta$-D-glucopyranoside (6).** To a −78 °C solution of **12** (442.8 mg, 0.869 mmol) in 20 mL of $CH_2Cl_2$ was added *m*-CPBA (220.6 mg, 68% purity, 0.869 mmol). The reaction was allowed to warm to −5 °C over 2 h and quenched with 100 $\mu$L of $Me_2S$. The reaction was poured into 100 mL of saturated $NaHCO_3$, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 mL). The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated. Purification of the residue by flash chromatography gave 449.1 mg (98%) of **6** as an oil (~1.5:1 mixture of sulfoxide isomers): $R_f$ 0.38 (50% EtOAc/petroleum ether); HR-MS (FAB) calcd for $C_{22}H_{27}N_3O_{10}SNa$ [M + $Na^+$] 548.1315, found 548.1309.

**2-(4-Azidobutyryl)-3,4,6-tri-*O*-acetyl-$\beta$-D-glucopyranosyl-2,6-dimethoxyphenol (7).** Phenyl 2-(4-azidobutyryl)-3,4,6-tri-*O*-acetyl-1-sulfinyl-$\beta$-D-glucopyranoside (**6**) (51.8 mg, 0.0986 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (40.8 mg, 0.197 mmol) were azeotroped three times with toluene. Flame-dried 4-Å sieves and a stir bar were added to the flask, followed by 4 mL of $CH_2Cl_2$. This solution was stirred for 45 min and then cooled to −78 °C. Next, 166 $\mu$L of a stock solution containing 100 $\mu$L of $Tf_2O$ and 900 $\mu$L of $CH_2Cl_2$ was added (0.0986 mmol of $Tf_2O$). The reaction was warmed to −60 °C, maintained at this temperature for 20 min, and then cooled back to −78 °C. 2,6-Dimethoxyphenol (8.6 mg, 0.0558 mmol) was dissolved in 1 mL of $CH_2Cl_2$, and $BF_3{\cdot}Et_2O$ (63 $\mu$L, 0.493 mmol) was added. This solution was added to the activated sulfoxide by syringe. The reaction was allowed to warm to −55 °C and then poured into 25 mL of saturated $NaHCO_3$ and stirred for 5 min. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 25 mL). The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (35% EtOAc/petroleum ether) to give 19.0 mg (62%) of **7**: $R_f$ 0.43 (40% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.04 (t, $J$ = 8 Hz, 1H, $H_a$ on phenol), 6.58 (d, $J$ = 8 Hz, 2H, $H_b$ on phenol), 5.24−5.36 (m, 3H, H2, H3, H4), 5.10 (d, $J$ = 7 Hz, 1H, H1), 4.26 (dd, $J$ = 12, 5 Hz, 1H, H6), 4.11 (dd, $J$ = 12, 2.5 Hz, 1H, H6′), 3.82 (s, 6H, 2 × OMe), 3.67−3.69 (m, 1H, H5), 3.32 (t, $J$ = 7 Hz, 2H), 2.39 (t, $J$ = 7 Hz, 2H), 2.03 (s, 3H, acetate), 2.02 (s, 6H, 2 acetates), 1.82−1.86 (m, 2H); $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ 171.8, 171.3, 171.1, 170.1, 154.0, 135.1, 125.6, 106.3, 101.8, 73.8, 72.9, 72.6, 69.3, 63.0, 57.0, 51.1, 31.6, 24.8, 21.4(3); HR-MS (FAB) calcd for $C_{24}H_{31}N_3O_{12}Na$ [M + $Na^+$] 576.1805, found 576.1805.

**3,4,6-Tri-*O*-acetyl-$\beta$-D-glucopyranosyl-2,6-dimethoxyphenol (13).** A solution of **7** (25.6 mg, 0.0463 mmol) in 5 mL of HPLC grade dioxane was heated to reflux, and $Ph_3P$ (62 mg, 0.236 mmol) was added. After 30 min, 1 mL of $H_2O$ was added, and refluxing was continued for a further 2 h. The solution was then cooled, 1 mL of BuOH was added, and the reaction was concentrated. Purification by flash chromatography with 5% MeOH/$CH_2Cl_2$ followed by flash chromatography with 50% EtOAc/petroleum ether gave 13.1 mg (64%) of **13** as a white solid: $R_f$ 0.15 (50% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.09 (t, $J$ = 8.5 Hz, 1H, $H_a$ on phenol), 6.62 (d, $J$ = 8.5 Hz, 2H, $H_b$ on phenol), 5.18 (apt, $J$ = 9.5 Hz, 1H, H3), 5.11 (apt, $J$ = 9.5 Hz, 1H, H4), 4.60 (d, $J$ = 8 Hz, 1H, H1), 4.28 (dd, $J$ = 12, 5 Hz, 1H, H6), 4.16 (dd, $J$ = 12, 2.5 Hz, 1H, H6′), 4.10 (bs, 1H, C2 OH), 3.91 (dd, $J$ = 9.5, 8.0 Hz, 1H, H2), 3.87 (s, 6H, 2 × OMe), 3.67−3.71 (m, 1H, H5), 2.11 (s, 3H, acetate), 2.08 (s, 3H, acetate), 2.03 (s, 3H, acetate); $^{13}$C NMR ($CDCl_3$, 500 MHz) $\delta$ 170.9, 170.7, 169.9, 153.1, 135.8, 125.6, 106.6, 105.6, 74.6, 72.7, 72.6, 68.7, 62.6, 56.5, 21.1, 21.0, 20.9; HR-MS (FAB) calcd for $C_{20}H_{26}O_{11}Na$ [M + $Na^+$] 465.1373, found 465.1390.

***N*-Alloc-tri-*O*-allyl-di-*O*-acetyl Vancomycin Aglycon Allyl Ester (14).** Vancomycin hydrochloride (3.0 g, 2 mmol) was dissolved in 25 mL of water and 25 mL of dioxane. $NaHCO_3$ (554 mg, 6.6 mmol) in 10 mL of water was added to the reaction solution, followed by *N*-(allyloxycarbonyloxy) succinimide (2 g, 8 mmol) in 10 mL of dioxane at room temperature. The reaction was stirred at room temperature for 3 h and then poured into 1000 mL of acetone. The white suspension was divided into four centrifuge tubes and centrifuged at 4000 rpm for 5 min. The precipitate was collected to give 3.8 g of *N,N′*-dialloc vancomycin as a white solid. A portion of this white solid (2.7 g) was subjected to the next reaction without further purification: $R_f$ 0.4 ($CHCl_3$/MeOH/$H_2O$ = 3/2/0.5).

The crude *N,N′*-dialloc vancomycin (2.7 g) from the previous reaction was dissolved in 10 mL of DMF and stirred at room temperature. Ground $KHCO_3$ (284 mg, 2.84 mmol) was added to the reaction solution. The suspension was stirred at reduced pressure for 30 min, and then allyl bromide (175 $\mu$L, 2.02 mmol) was added. The reaction was stirred for 5 h at room temperature and poured into a mixture of 200 mL of acetone and 800 mL of diethyl ether. This white suspension was divided into four centrifuge tubes and centrifuged at 5000 rpm for 15 min. The precipitate was collected and dried to give 3 g of crude *N,N′*-dialloc vancomycin allyl ester. This crude material was subjected to the next reaction without further purification: $R_f$ 0.12 (20% MeOH/$CHCl_3$).

To a solution of *N,N′*-dialloc vancomycin allyl ester (3 g) in 15 mL of DMF was added $Cs_2CO_3$ (2.3 g, 7.1 mmol). This suspension was stirred under reduced pressure for 15 min, and then allyl bromide (1.3 mL, 14.2 mmol) was added. The reaction was stirred at room temperature overnight until TLC indicated complete reaction. The suspension was precipitated with 200 mL of water. The white suspension was divided into four centrifuge tubes and centrifuged at 5000 rpm for 60 min. The precipitate was collected and loaded onto a silica gel column (50 mm × 15 cm). Elution with 200 mL of 5% MeOH/$CHCl_3$ and then 500 mL of 20% MeOH/$CHCl_3$ provided 2 g of semipure *N,N′*-dialloc-tri-*O*-allyl vancomycin allyl ester as a white solid: $R_f$ 0.65 (20% MeOH/$CHCl_3$); HR-MS(FAB) calcd for $C_{86}H_{99}N_9O_{28}Cl_2Na$ [M + $Na^+$] 1798.5874, found 1798.5844; $^1$H NMR, see Supporting Information.

To a solution of 232 mg of semipure *N,N'*-dialloc-tri-*O*-allyl vancomycin allyl ester in 4 mL of acetic acid were added thiophenol (75 $\mu$L, 0.730 mmol) and 2 mL of 3% HBr in acetic acid. The reaction was stirred at room temperature for 15 min and then poured into 100 mL of $H_2O$. The white precipitate was isolated by centrifugation. Purification of the precipitate by flash chromatography (0 to 5% MeOH/$CH_2Cl_2$) yielded 121 mg (63% over 4 steps from vancomycin) of *N*-alloc-tri-*O*-allyl vancomycin aglycon allyl ester as a white solid: $R_f$ 0.34 (10% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{69}H_{72}N_8O_{19}Cl_2Na$ [M + $Na^+$] 1409.4188, found 1409.4220; $^1H$ NMR, see Supporting Information.

To a solution of *N*-alloc-tri-*O*-allyl vancomycin aglycon allyl ester (1.247 g, 0.898 mmol) in 20 mL of DMF were added $Cs_2CO_3$ (585 mg, 1.80 mmol) and PMBCl (609 $\mu$L, 4.49 mmol). The reaction was stirred at room temperature overnight and then concentrated to an oil. This oil was purified by flash chromatography (0 to 5% MeOH/$CHCl_3$) to give 1.338 g (99%) of *N*-alloc-tri-*O*-allyl-*O*-PMB vancomycin aglycon allyl ester as a white solid: $R_f$ 0.45 (10% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{77}H_{80}N_8O_{20}Cl_2Na$ [M + $Na^+$] 1529.4764, found 1529.4833; $^1H$ NMR, see Supporting Information.

To a solution of *N*-alloc-tri-*O*-allyl-*O*-PMB vancomycin aglycon allyl ester (150 mg, 0.0995 mmol) in 2 mL $CH_2Cl_2$ were added pyridine (40 $\mu$L, 0.497 mmol) and acetic anhydride (28 $\mu$L, 0.298 mmol), followed by a catalytic amount of DMAP (2 mg). The reaction was stirred at room temperature for 6 h and then quenched with 1 mL of MeOH and concentrated in vacuo. The resulting oil was purified by flash chromatography (0 to 5% MeOH/$CHCl_3$) to give 125 mg (79%) of *N*-alloc-tri-*O*-allyl-*O*-PMB-di-*O*-acetyl vancomycin aglycon allyl ester as a white solid: $R_f$ 0.5 (10% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{81}H_{84}N_8O_{22}Cl_2Na$ [M + $Na^+$] 1613.4975, found 1613.5036; $^1H$ NMR, see Supporting Information.

To a solution of *N*-alloc-tri-*O*-allyl-*O*-PMB-di-*O*-acetyl vancomycin aglycon allyl ester (125 mg, 0.0785 mmol) in 5 mL of $CH_2Cl_2$ were added 0.5 mL of TFA at room temperature. After 10 min, 25 mL of toluene was added, and the reaction was concentrated in vacuo. The residual white solid was purified by flash chromatography (5% MeOH/$CH_2Cl_2$) to give 98 mg (85%) of **14** as a white solid: $R_f$ 0.47 (10% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{73}H_{76}N_8O_{21}Cl_2Na$ [M + $Na^+$] 1493.4400, found 1493.4368; $^1H$ NMR, see Supporting Information.

***N*-Alloc-tri-*O*-allyl-penta-*O*-acetyl Vancomycin Pseudoaglycon Allyl Ester (16).** DTBMP (45.1 mg, 0.220 mmol) and **6** (60.7 mg, 0.116 mmol) were azeotroped three times with toluene in a 25-mL round-bottom flask. Flame-dried 4-Å molecular sieves and 3 mL of $CH_2Cl_2$ were added to the flask. The solution was stirred for 45 min and then cooled to −78 °C. $Tf_2O$ (194 $\mu$L of a stock solution containing 100 $\mu$L of $Tf_2O$ and 900 $\mu$L of $CH_2Cl_2$, 0.116 mmol of $Tf_2O$) was added, and the reaction was allowed to warm to −60 °C over 15 min and maintained at that temperature for 20 min. The reaction was then cooled back to −78 °C, and **14** (52.5 mg, 0.0357 mmol) was added with $BF_3{\cdot}Et_2O$ (90 $\mu$L, 0.713 mmol) in 1 mL of $CH_2Cl_2$. The reaction was allowed to warm to 0 °C over 1.5 h and then filtered through a plug of silica gel into a flask containing 200 $\mu$L of pyridine. The filtrate was concentrated, and the residue was purified by flash chromatography (50% EtOAc/petroleum ether then 5% MeOH/$CH_2Cl_2$) to give 56.1 mg of crude **15** as a white solid. This material was dissolved in 4.5 mL of HPLC grade dioxane and heated to reflux. $Ph_3P$ (34 mg, 0.129 mmol) was added, and the reaction was refluxed for an additional 30 min. Then 1 mL of $H_2O$ was added, and refluxing was continued for a further 2 h. At this point, the reaction was cooled and concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/petroleum ether then 5% MeOH/$CH_2Cl_2$) and then radial chromatography (5% MeOH/$CH_2Cl_2$) to give 24.7 mg of semipure **16**. Purification by reversed-phase HPLC (Phenomenex LUNA C18 column, 21 × 25 mm, 5 $\mu$m particle size, using a linear gradient of 70 to 90% $CH_3CN/H_2O$ with 0.1% HOAc over 30 min, flow rate = 7 mL/min, retention time = 19 min) gave 7.9 mg (13%) of **16** as a white solid: $R_f$ 0.21 (5% MeOH/$CH_2Cl_2$); HR-MS (FAB) calcd for $C_{85}H_{92}N_8O_{29}Cl_2Na$ [M + $Na^+$] 1781.5274, found 1781.5245; $^1H$ NMR, see Supporting Information.

**Reconstruction of Vancomycin (1).** The pseudoaglycon **16** (19 mg, 0.0108 mmol) was azeotroped with toluene three times (1 mL each), dissolved in 1 mL of $CH_2Cl_2$, and then cooled to −78 °C. $BF_3{\cdot}OEt_2$ (2 $\mu$L, 0.0168 mmol) was added, followed by triflic anhydride (4 $\mu$L, 0.0247 mmol). A solution of sulfoxide **17** (20 mg, 0.0509 mmol) in 0.5 mL of $Et_2O$ was added to the reaction over 1 min. The reaction was allowed to warm to −20 °C over 1 h and then quenched by addition of a solution of 100 $\mu$L of methanol and 100 $\mu$L of DIEA. The solvent was removed under reduced pressure, and the residue was purified on a silica gel column (10 mm × 10 cm), eluting with $CHCl_3$, followed by 5% MeOH/$CHCl_3$ to give 20 mg of crude product as a white solid. This solid was repurified by reversed-phase HPLC using a Phenomenex LUNA C18 column (21.2 × 250 mm), 5 $\mu$m particle size, eluting with a 30-min linear gradient of 80% acetonitrile/0.1% acetic acid in water to 100% acetonitrile/0.1% acetic acid, flow rate of 8 mL/min, and ultraviolet (UV) detection at 285 nm. The peak at 12 min was collected and concentrated to give 4.3 mg (22%) of recovered **16**, while the peak at 13 min was collected and concentrated to give 13.3 mg (60%) of *N,N'*-dialloc-tri-*O*-allyl-hexa-*O*-acetyl vancomycin allyl ester as a white solid: $R_f$ 0.2 (5% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{98}H_{111}N_9O_{34}Cl_2Na$ [M + $Na^+$] 2050.6508, found 2050.6458; $^1H$ NMR: see Supporting Information.

*N,N'*-Dialloc-tri-*O*-allyl-hexa-*O*-acetyl vancomycin allyl ester (5 mg, 0.00247 mmol) was dissolved in 500 $\mu$L of a solution of allyl alcohol/methanol/THF = 1:1:1 containing 5% $NH_2NH_2$.[26] The reaction was stirred at room temperature for 6 h and then quenched by addition of 100 $\mu$L of acetic acid. All solvents were removed under reduced pressure, and the residue was purified by reversed-phase HPLC using a Phenomenex LUNA C18 column (21.2 × 250 mm), 5 $\mu$m particle size, eluting with a 30-min linear gradient of 50% acetonitrile/0.1% acetic acid in water to 70% acetonitrile/0.1% acetic acid in water, flow rate of 8 mL/min, and ultraviolet (UV) detection at 285 nm. The fractions containing the desired product were collected and concentrated to give 3.1 mg (70%) of *N,N'*-dialloc-tri-*O*-allyl vancomycin allyl ester as a white solid: $R_f$ 0.65 (20% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{86}H_{99}N_9O_{28}Cl_2Na$ [M + $Na^+$] 1798.5874, found 1798.5844; $^1H$ NMR, see Supporting Information.

*N,N'*-Dialloc-tri-*O*-allyl vancomycin allyl ester (3.9 mg, 0.00220 mmol) was dissolved in 0.5 mL of DMF, and then 0.5 mL of acetic acid was added. A small amount of palladium dichloride−bis-triphenylphosphine (~2 mg) was added, and the reaction vessel was filled with nitrogen. To this mixture was added, with vigorous stirring, tributyltin hydride (two additions of 50 $\mu$L each at 5-min intervals). The crude reaction mixture was precipitated with 30 mL of acetone in a 50-mL centrifuge tube. The suspension was centrifuged, and the supernatant was decanted to give a white solid. This white solid was dissolved in 5 mL of water and kept at 0 °C overnight. The resulting suspension was filtered through a disposable 13-$\mu$m syringe filter (Whatman Inc.) to remove tin polymers, and the filtrate was concentrated. The residual solid was purified by reversed-phase HPLC using a Phenomenex LUNA C18 column (21.2 × 250 mm), 5 $\mu$L particle size, eluting with 0.1% acetic acid in water for 5 min and then a 30-min linear gradient of 0.1% acetic acid in water to 20% acetonitrile/0.1% acetic acid in water, flow rate of 7 mL/min, and ultraviolet (UV) detection at 285 nm. The fractions containing the product were combined and concentrated to give 2.6 mg (79%) of vancomycin (**1**) as the acetic acid salt, a white solid. The synthetic vancomycin was identical to an authentic sample of vancomycin by TLC, MS (ESI), $^1H$ NMR, and analytical HPLC (Phenomenex LUNA C18 column (4.6 × 250 mm), 5 $\mu$m particle size, eluting with 0.1% TFA in water for 2 min and then a 28-min linear gradient of 0.1% TFA in water to 20% acetonitrile/0.1% TFA in water, flow rate of 1 mL/min, and ultraviolet (UV) detection at 285 nm; vancomycin had a retention time of 28 min).

**Vancomycin Aglycon (18).**[22] To a solution of vancomycin hydrochloride (3.7 g, 2.50 mmol) in 35 mL of water was added 3 mL of concentrated HCl (aqueous). The reaction was refluxed for 5 min and then cooled to room temperature. The white precipitate was collected by suction filtration using a glass funnel equipped with a medium frit. After filtration, the precipitate was washed with acetone and dried to

(26) The allyl alcohol was included in the reaction in order to prevent the reduction of the allyl protecting groups on vancomycin by diimide, which may be present in hydrazine.

give a brown solid. The crude product was used without further purification: $R_f$ 0.05 ($CHCl_3$/MeOH/$H_2O$ = 3/2/0.5).

***N*-Alloc-*O*-PMB Vancomycin Aglycon Allyl Ester (19).** The crude vancomycin aglycon **18** was dissolved in 20 mL of water and 25 mL of dioxane. $NaHCO_3$ (1.07 g, 12.75 mmol) in 10 mL of water was added to the solution, followed by *N*-(allyloxycarbonyloxy) succinimide (2 g, 8 mmol) in 10 mL of dioxane. The reaction was stirred at room temperature for 3 h and then poured into 1000 mL of acetone. The white suspension was divided into four centrifuge tubes and centrifuged at 4000 rpm for 5 min. The precipitate was collected to give 3 g of *N*-alloc vancomycin aglycon as a white solid. This material was subjected to the next reaction without further purification: $R_f$ 0.3 ($CHCl_3$/MeOH/$H_2O$ = 3/2/0.5).

The crude *N*-alloc vancomycin aglycon (200 mg) from the previous reaction was dissolved in 3 mL of DMF and stirred at room temperature. Ground $KHCO_3$ (50 mg, 0.5 mmol) was added to the solution. The suspension was stirred at reduced pressure for 30 min, and then allyl bromide (70 $\mu$L, 0.835 mmol) was added. The reaction was stirred for 3 h and then quenched by addition of 1 mL of acetic acid. The solvent was removed, and the residue was purified by flash chromatography to give 50 mg (16%, not optimized) of *N*-alloc vancomycin aglycon allyl ester as a white solid: $R_f$ 0.32 (20% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{60}H_{61}N_8O_{19}Cl_2$ [M + $H^+$] 1267.3430, found 1267.3375; $^1$H NMR, see Supporting Information.

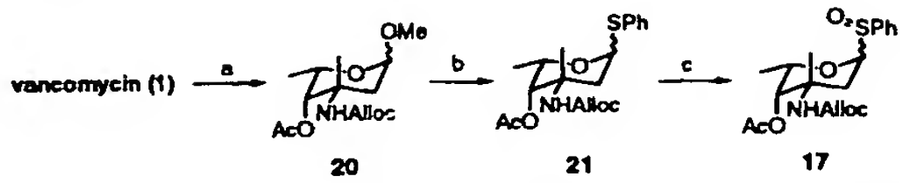
To a solution of *N*-alloc vancomycin aglycon allyl ester (7 mg, 0.00552 mmol) in 2 mL of DMF were added $Cs_2CO_3$ (5 mg) and PMBCl (10 $\mu$L). The reaction was stirred for 2 h and then quenched by addition of 1 mL of acetic acid, followed by 25 mL of water. The precipitate was collected by suction filtration using a glass funnel equipped with a medium frit. The precipitate was purified by reversed-phase HPLC using a Phenomenex LUNA C18 column (21.2 × 250 mm), 5 $\mu$m particle size, eluting with a linear gradient of 30% acetonitrile/0.1% acetic acid in water to 65% acetonitrile/0.1% acetic acid in water over 40 min and then 65% acetonitrile/0.1% acetic acid in water to 70% acetonitrile/0.1% acetic acid in water over 5 min, flow rate of 7 mL/min, and ultraviolet (UV) detection at 285 nm. The fractions containing the product were combined and concentrated to give to give 5 mg (71%) of **19** as a white solid: $R_f$ 0.51 (20% MeOH/$CHCl_3$); HR-MS (FAB) calcd for $C_{68}H_{68}N_8O_{20}Cl_2Na$ [M + $Na^+$] 1409.3824, found 1409.3749; $^1$H NMR, see Supporting Information.

***N*-Alloc-tri-*O*-allyl-di-*O*-acetyl Vancomycin Aglycon Allyl Ester (14).** To a solution of *N*-alloc-*O*-PMB vancomycin aglycon allyl ester (10 mg, 0.00721 mmol) in 1 mL of DMF was added $Cs_2CO_3$ (13.5 mg, 0.0416 mmol). This suspension was stirred under reduced pressure for 15 min, and then allyl bromide (12 $\mu$L) was added. The reaction was stirred at room temperature for 7 h and then quenched by addition of 1 mL of acetic acid, followed by 25 mL of water. The precipitate was collected by suction filtration using a glass funnel equipped with a medium frit. The precipitate was then purified by reversed-phase HPLC using a Phenomenex LUNA C18 column (21.2 × 250 mm), 5 $\mu$m particle size, eluting with a 30-min linear gradient of 50% acetonitrile/0.1% acetic acid in water to 90% acetonitrile/0.1% acetic acid in water, flow rate of 7 mL/min, and UV detection at 285 nm. The fractions containing the pure product were combined and evaporated to give 6 mg (59%) of *N*-alloc-tri-*O*-allyl-*O*-PMB vancomycin aglycon allyl ester as a white solid. This material was identical by TLC, ESI-MS, and $^1$H NMR to the compound obtained previously by the other route (degradation of protected vancomycin derivative).

The synthesis of **14** from *N*-alloc-tri-*O*-allyl-*O*-PMB vancomycin aglycon allyl ester was described above.

**Methyl 3-(*N*-Allyloxycarbonyloxy)-2,3,6-trideoxy-3-*C*-methyl-α,β-L-*lyxo*-hexopyranoside (20)** (Scheme 4). To a solution of *N*,*N*′-dialloc vancomycin (1.0 g crude) in 8 mL of methanol was added 1.2 mL of concentrated aqueous HCl. The reaction was stirred at room temperature for 10 min, and then the solvent was removed in vacuo. The residual green oil was suspended in 200 mL of acetone and then centrifuged at 4000 rpm for 5 min. The clear supernatant was collected and concentrated to give a green oil. This oil was loaded onto a silica gel column and eluted with EtOAc to give crude *N*-alloc-vancosamine methyl glycoside (188 mg) as a clear oil. This oil was subjected to the next reaction without further purification: $R_f$ 0.15 (30% EtOAc/petroleum ether).

**Scheme 4**[a]




[a] Conditions: (a) (i) 4 equiv of alloc-succinimide, 3 equiv of $NaHCO_3$, $H_2O$/dioxane = 1/1, rt, 3 h; (ii) 1 M HCl/MeOH, 10 min, rt; (iii) 3 equiv of $Ac_2O$, pyridine, 0.1 equiv of DMAP, rt, 12 h, 56% over three steps; (b) 1.2 equiv of PhSH, 3 equiv of $BF_3$·$OEt_2$, $CH_2Cl_2$, rt, 15 min, 88%; (c) 1 equiv of mCPBA, $CH_2Cl_2$, −78 to −20 °C, 1 h, then 10 equiv of DMS, 86%.

The *N*-alloc-vancosamine methyl glycoside (188 mg) was dissolved in 3 mL of pyridine. DMAP (0.2 mg) was added to the reaction, followed by acetic anhydride (0.5 mL). After 12 h, TLC showed complete reaction. The reaction was quenched by addition of 0.5 mL of methanol, and the solvents were removed under reduced pressure. The residue was loaded onto a silica gel column (20 mm × 14 cm) and eluted with 30% EtOAc/petroleum ether to give 104 mg (56%, three steps from vancomycin) of **20** as a clear oil (α:β = 2:1). α anomer: $R_f$ 0.3 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.92−5.86 (m, 1H), 5.25 (dd, $J$ = 1.5, 17.4 Hz, 1H), 5.20 (dd, $J$ = 1.2, 10.4 Hz, 1H), 4.97 (s, 1H, H-4), 4.80 (d, $J$ = 4.6 Hz, 1H, H-1), 4.75 (s, 1H), 4.53 (m, 1H), 4.46 (dd, $J$ = 5.8, 13 Hz, 1H), 4.10 (q, $J$ = 6.4 Hz, 1H, H-5), 3.33 (s, 3H), 2.16 (s, 3H). 2.12 (d, $J$ = 14.3 Hz, 1H, H-2), 1.97 (dd, $J$ = 4.6, 13.8 Hz, 1H, H-2′), 1.71 (s, 3H), 1.15 (d, $J$ = 6.4 Hz, 3H, H-6); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 171.8, 157.0, 133.6, 118.4, 99.0, 74.5, 65.9, 63.5, 55.8, 53.7, 36.4, 24.7, 21.5, 18.0. β anomer: $R_f$ 0.27 (30% EtOAc/petroleum ether); $^1$H NMR ($CDCl_3$, 500 MHz) δ 5.93−5.86 (m, 1H), 5.26 (d, $J$ = 17 Hz, 1H), 5.21 (d, $J$ = 10.4 Hz, 1H), 5.02 (s, 1H, H-4), 4.75 (bs, 1H), 4.58−4.52 (m, 2H), 4.47−4.44 (dd, $J$ = 5.5, 12.8 Hz, 1H), 3.87 (q, $J$ = 6.4 Hz, 1H, H-5), 3.52 (s, 3H), 2.15 (s, 3H), 2.10 (t, $J$ = 9 Hz, 1H), 2.05 (d, $J$ = 14 Hz, 1H), 1.625 (s, 3H), 1.20 (d, $J$ = 6.4 Hz, 3H, H-6); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 171.5, 155.0, 133.5, 118.6, 100.2, 77.1, 69.1, 66.0, 57.3, 55.2, 39.0, 22.9, 21.5, 18.0; HR-MS (FAB) calcd for $C_{14}H_{23}NO_6Na$ [M + $Na^+$] 324.1423, found 324.1416.

**Phenyl 3-(*N*-Allyloxycarbonyloxy)-4-*O*-acetyl-1-thio-2,3,6-trideoxy-3-*C*-methyl-α,β-L-*lyxo*-hexopyranoside (21)** (Scheme 4). Compound **20** (170 mg, 0.569 mmol) was azeotroped with toluene three times and then dissolved in 7 mL of $CH_2Cl_2$. PhSH (117 $\mu$L, 1.14 mmol) was added, followed by $BF_3$·$OEt_2$ (77 $\mu$L, 0.626 mmol). TLC showed complete reaction after 60 min. The reaction was quenched by addition of 20 mL of saturated $NaHCO_3$. The $CH_2Cl_2$ layer was separated, and the aqueous layer was further extracted with $CH_2Cl_2$ (3 × 20 mL). The $CH_2Cl_2$ layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give a clear oil. This oil was loaded onto a silica gel column (30 mm × 14 cm) and eluted with 30% EtOAc/petroleum ether to give 190 mg (88%) of **21** as a white solid (α:β = 1:2): $R_f$ 0.40 (30% EtOAc/petroleum ether). β anomer: $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, 2H), 7.38−7.28 (m, 3H), 5.95−5.88 (m, 1H), 5.30 (dd, $J$ = 1.6, 17.4 Hz, 1H), 5.22 (dd, $J$ = 1.2, 10.4 Hz, 1H), 5.00−4.96 (m, 2H, H-4, H-1), 4.79 (s, 1H), 4.55 (m, 1H), 4.47 (dd, $J$ = 5.8, 13.2 Hz, 1H), 3.93 (q, $J$ = 6.4 Hz, 1H, H-5), 2.3 (d, $J$ = 12.3 Hz, 1H, H-2), 2.17 (s, 3H), 1.95 (t, $J$ = 12.5 Hz, 1H, H-2′), 1.65 (s, 3H), 1.23 (d, $J$ = 6.4 Hz, 3H, H-6); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 171.66, 155.00, 134.70, 133.45, 132.25, 131.73, 129.53, 128.19, 118.60, 81.81, 73.16, 71.89, 66.06, 55.20, 38.55, 21.49, 18.50. α anomer: $^1$H NMR ($CDCl_3$, 500 MHz) δ 7.60−7.50 (m, 2H), 7.37−7.20 (m, 3H), 5.95−5.88 (m, 1H), 5.63 (dd, $J$ = 2.5, 6.7 Hz, 1H, H-1), 5.32 (dd, $J$ = 1.2, 17.1 Hz, 1H), 5.23 (d, $J$ = 10.4 Hz, 1H), 5.00 (s, 1H, H-4), 4.90 (bs, 1H), 4.58−4.47 (m, 3H), 2.61−2.56 (m, 1H, H-2), 2.30−2.27 (dd, $J$ = 1.8, 14.3 Hz, 1H, H-2′), 2.19 (s, 3H), 1.79 (s, 3H), 1.19 (d, $J$ = 6.4, 3H, C-6 Me); $^{13}$C NMR ($CDCl_3$, 500 MHz) δ 171.58, 155.00, 136.55, 133.51, 132.26, 131.73, 129.59, 127.85, 118.57, 83.64, 74.67, 66.05, 64.93, 54.18, 37.85, 24.65, 17.66; HR-MS (EI) calcd for $C_{19}H_{25}NO_5SNa$ [M + $Na^+$] 402.1351, found 402.1360.

**Phenyl 3-(*N*-Allyloxycarbonyloxy)-4-*O*-acetyl-1-sulfinyl-2,3,6-trideoxy-3-*C*-methyl-L-*lyxo*-hexopyranoside (17)** (Scheme 4). The vancosamine sulfide **21** (78 mg, 0.207 mmol) was dissolved in 10 mL of $CH_2Cl_2$ and cooled to −78 °C. *m*-CPBA (39.8 mg of 64% purity, 0.207 mmol) was added, and the reaction was slowly warmed to −20 °C over 1 h. TLC showed complete reaction. The reaction was quenched by addition of 100 μL of dimethyl sulfide. Ten milliliters of saturated $NaHCO_3$ was added, and the $CH_2Cl_2$ layer was extracted. The aqueous layer was further extracted with $CH_2Cl_2$ (3 × 10 mL). The $CH_2Cl_2$ layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to a clear oil. This oil was loaded onto a silica gel column (30 mm × 10 cm) and eluted with 60% EtOAc/petroleum ether to give 70 mg (86%) of **17** as a white solid: $R_f$ 0.12 and 0.10 (40% EtOAc/petroleum ether).

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**Supporting Information Available:** $^1H$ NMR (500 MHz) spectra of nine vancomycin intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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